## REMARKS

Claims 2-9 are pending. Claims 2-8 are under examination. Withdrawn claim 9 is being maintained of record pending the filing of a divisional application.

Claim 8 has been amended to overcome the informality discussed on page 5 of the Office Aciton. The Office Action stated that a Markush group should have the word "and" between the last two items. Original claim 8 did contain the word "and" between the penultimate item, foot ulceration, and the last item, cataracts. The phrase ",associated with diabetes" at the end of the claim modified each of the preceding items in the list of symptoms. To improve the clarity of the claim the modifying phrase has been inserted after each item in the list. The Office Action also noted that the use of a colon is not needed in a Markush group. It has been deleted.

## ELECTION/RESTRICTION

The Office has required restriction between two allegedly distinct inventions: Group I, claims 2-8, drawn to a method of treatment; and Group II, claim 9, drawn to a pharmaceutical composition. The Office has also required election of a single disclosed species to which the claims will be restricted if no generic claim is finally held to be allowable.

Applicants hereby confirm their November 13, 2006 telephone election. In response to the restriction requirement, applicants elect Group I (claims 2-8) without traverse. In response to the election of species requirement, applicants elect 4-(4-benzyloxy-3-chlorophenyl)-4-oxobutanoic acid. Claims 2-8 read on the elected species.

**INVENTION IS ENABLED**

Claims 2-8 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the specification. This rejection is respectfully traversed.

In the instant case applicant has disclosed certain of compounds, has described how to make such compounds, has stated what diseases they are useful for treating, has taught how to formulate and administer such compounds, as well as their dosages. And yet the Office asserts its "position that one skilled in the art could not practice the invention without undue experimentation." (Office Action, page 6). In view of the extensive disclosure in this application, the rejection's assertion of undue experimentation presumably means that the Office does not believe that the compounds recited in the claims are useful in treating the recited diseases when administered as described in the specification.

The Office bears the burden of establishing that an invention does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated by the CCPA in In re Marzocchi:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

(In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, ___) (underlining added). It is not sufficient for the Office to simply assert that it doubts the correctness of the statements in the disclosure. The Office must back up its doubts with evidence or reasoning. Again from In re Marzocchi:

> "In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

(In re Marzocchi, 439 F.2d at 224, 169 USPQ at ___) (internal citations omitted) (underlining added). The only reasoning presented by the rejection is the alleged unpredictability of the pharmaceutical art in general. The rejection stated:

> "It is generally recognized in the art that biological compounds often react unpredictably under different circumstances. The relative skill of the artisan or [sic] the unpredictability of the pharmaceutical art is very high."

(Office Action, page 3) (internal citations omitted). But that does not constitute adequate reasoning to support an enablement rejection. If the mere assertion that the pharmaceutical art is unpredictable would be accepted as sufficient reasoning, it would mean that in the case of all biological and pharmaceutical inventions applicants would have the burden of demonstrating enablement rather than the Office having the burden of demonstrating that an invention is not enabled. And that would be contrary to the law as articulated in Marzocchi above.

WO 02/100341 (of record) tested and demonstrated the activity of a representative number of compounds within a genus. The person of ordinary skill in the art would accept that other compounds within the genus would possess activity similar to the compounds tested.

The rejection singled out cachexia as a disorder whose treatment is allegedly not enabled by the specification. Compounds of the invention reverse insulin resistance associated with diabetes and metabolic disease. While insulin resistance is often associated with obesity (especially in the setting of concurrent hyperinsulinemia), insulin resistance is

also a component of disease states involving weight loss (abstract of Wedick NM, et al. (2001) Insulin resistance precedes weight loss in adults without diabetes. American Journal of Epidemiology 153:1199-1205; abstract of Rofe et al., (1994) Altered insulin response to glucose in weight-losing cancer patients. Anticancer Research 14:647-650.) (enclosed with the Form PTO/SB/08a submitted concurrently herewith).

Cachexia involves muscle wasting associated with disease states including cancer, systemic inflammation, infection and aging. A key element in cachexia is impaired insulin sensitivity, especially in muscle. Cancer patients with weight loss often have impaired glucose tolerance, a sign of insulin resistance (Rofe et al., 1994 (abstract); abstract of Tayek, (1992) A review of cancer cachexia and abnormal glucose metabolism in humans with cancer. Journal of the American College of Nutrition 11:445-456) (enclosed with the Form PTO/SB/08a submitted concurrently herewith). Insulin signaling in muscle inhibits proteolysis; either insulin deficiency or insulin resistance disinhibits proteolysis, leading to loss of muscle mass. Combined insulin deficiency and resistance occurs in uncontrolled Type 1 diabetes and in cancer cachexia.

An additional link between insulin and body weight dysregulation in both obesity and cachexia is tumor necrosis factor alpha (TNFα). TNFα was originally known as "cachectin" due to its role in cachexia or muscle wasting and weight loss induced by infection and cancer. However, TNFα expressed in adipose tissue induces insulin resistance and obesity (abstract of Argiles et al., (1997) Journey from cachexia to obesity by TNF. The FASEB Journal 11:743-751) (enclosed with the Form PTO/SB/08a submitted concurrently herewith). TNFα is one of the causes of insulin resistance in both diabetes and cachexia (abstract of de Alvaro et al., (2004) Tumor Necrosis Factor α produces insulin resistance in skeletal muscle by activation of Inhibitor κB Kinase in a p38 MAPK-dependent manner (2004) Tumor Necrosis Factor α produces insulin resistance in skeletal muscle by activation of Inhibitor κB Kinase in a p38 MAPK-

dependent manner) (enclosed with the Form PTO/SB/08a submitted concurrently herewith).

Compounds of the invention reverse insulin resistance associated with diabetes and obesity, and can attenuate weight gain in that situation. However, by addressing insulin resistance in situations where muscle wasting is occurring, including insulin deficiency states, compounds of the invention attenuate the severity of cachexia, both prophylactically and therapeutically.

In view of the foregoing, applicants respectfully submit that the enablement rejection has been overcome.

**INVENTION IS NONOBVIOUS**

Claims 2-8 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 6,143,787 (Moinet et al.). The rejection is respectfully traversed.

The compounds recited in the pending claims are unsubstituted at the position where the Moinet compound is substituted by $-CH_2-B$. Moinet is cited as teaching that B can be, among other things, an alkyl group having from 1 to 14 carbon atoms. The rejection pretends that this feature supports the rejection. The rejection states, "However, since the Group B of formula (I) [of Moinet] can be an alkyl group of 1-14 carbon atoms (column 1, line 24), the substitution of an alkyl group with hydrogen at the 2-position of the oxobutanoic acid is obvious." (Office Action, page 10). Contrary to the position of the rejection, hydrogen is not an adjacent homolog of alkyl having from 2 to 15 carbon atoms. Moinet could have easily drawn formula I in such a way that $-CH_2-B$ was replaced by -B and could have included hydrogen as a possible value for the variable B. The fact that Moinet et al. went out of their way to exclude not only compounds that are unsubstituted at the 2-position of the oxobutanoic acid moiety but even compounds that

are methyl-substituted (i.e. B is hydrogen) at the 2-position of the oxobutanoic acid moiety, undermines the basis of the rejection.

The rejection also relies on Moinet as allegedly teaching that "the treatment shows no sign of toxicity". (Office Action, page 10) (citing Moinet column 17, lines 56-57). This reliance is misplaced. In the passage cited by the Office Action Moinet states, "Products Nos. 5 and 6 administered orally at a dose of 200 mg/kg induced no sign of toxicity." (Moinet, (column 17, lines 56-57). But in the compounds bearing Moinet Product Nos. 5 and 6, B is phenyl, not the alkyl that the Office alleges is an obvious variant of hydrogen. In fact, B is not alkyl in any of the actual examples disclosed in Moinet. The person of ordinary skill in the art would have noticed that Moinet's teachings concerning compounds in which B was alkyl were untested. Accordingly, the person of ordinary skill in the art would have had less confidence that such compounds indeed possessed the desired activity and certainly would not have taken the flight of fancy necessary to extrapolate from such untested compounds to compounds in which $-CH_2-B$ was replaced by hydrogen.

Applicant respectfully submits that the obviousness rejection has been overcome and should be withdrawn.

**DOUBLE PATENTING REJECTIONS**

Claims 2-8 have been provisionally rejected on grounds of obviousness-type double patenting as allegedly being unpatentable over claims 6-13 of copending Application No. 10/553,936 (the '936 application) and claims 6-13 of copending Application No. 10/531,618 (the '618 application). The provisional obviousness-type double patenting rejections are respectfully traversed.

With respect to the '936 application the rejection alleged that the substitution of a keto group with an alkenyl double bond is obvious. The rejection stated that one having

ordinary skill in the art would have had "the expectation that the substitution of a keto group for a double bond would not significantly alter the analogous properties of the compound due to close structural similarity of the compounds." (Office Action, page 13). No reason is given to support the Office's conclusory position. To the contrary, the person of ordinary skill in the art would not have had a reasonable expectation that the compounds would have the same properties because the presence of the alkenyl double bond will result in a molecule having restricted rotation compared to the analogous compound having a keto-substitution.

Moreover, the position being taken by the Office in this provisional rejection is inconsistent with the position previously taken by the Office in U.S. Application No. 10/167,839 (the '839 application), now U.S. Patent No. 7,101,910. The '839 application claimed a genus of compounds (Formula I) that has a keto-subsitution at the position adjacent to the central phenyl ring and generically encompasses those claimed in the subject application and a genus of compounds (Formula XCI) that has an alkenyl double bond at the position adjacent to the central phenyl ring and is the same as those of the '936 application except for the length of the alkenyl chain. In the '839 application the Office required restriction between the claims directed to compounds of Formula I in which "A" was a phenyl ring and compounds of Formula XCI in which "A" was a phenyl ring. (Paper No. 12, dated September 30, 2003, in the '839 application). The restriction requirement in the '839 application is evidence that the compounds having a keto group adjacent to the central benzene ring recited in the claims of the subject application are patentably distinct from the analogous compounds having an alkenyl double bond at the same position.

With respect to the '618 application the rejection alleged that the substitution of a keto group with a hydroxyl group is obvious. The rejection stated, "One having ordinary skill in the art would have been motivated to substitute the keto group with a hydroxyl group with the expectation that the substitution would not significantly alter the analogous properties of the compound due to close structural similarity of the compounds." (Office

Action, pages 13-14). Contrary to the position of the rejection, the substitution of a planar carbonyl group with a tetrahedral alcohol will change both the geometery and the hydrogen-bonding properties and charge distribution of the molecule. Alcohols have both hydrogen-bond donor and acceptor properties, while the carbonyl oxygen acts as a hydrogen-bond acceptor. Accordingly, the person of ordinary skill in the art would not have had a reasonable expectation that changing keto to hydroxy would leave the properties unchanged.

The Office Action also stated that applicant has what the Examiner considers to be numerous copending applications allegedly encompassing the same or similar subject matter as the instant application, for example claims 1-44 and 46-66 of Application No. 11/535,779. The Office advised applicants to review all subject matter considered the same or similar and submit appropriate terminal disclaimer(s) (Office Action, page 14). Upon an indication of otherwise allowable subject matter applicants will consider filing a terminal disclaimer over Application No. 11/535,779. Applicants do not believe that an issue of double patenting exists between the subject application any other copending applications.

In a December 21, 2006 telephone conference the Examiner informed the undersigned that, after speaking with her supervisor, the Office is not able to provide general guidance as to what is meant by "similar" in the passage of the Office Action referred to above. Gleaning what guidance they could about the intended meaning of "similar" from the provisional obviousness-type double patenting rejections set forth in the Office Action, applicants filed an Information Disclosure Statement on March 30, 2007.

## CONCLUSION

In view of the amendment and the preceding remarks, applicants respectfully request reconsideration and withdrawal of all objections and rejections.

It is believed that no fee is required in connection with the filing of this Amendment. If any fee is required, the Commissioner is hereby authorized to charge the amount of such fee to Deposit Account No. 50-1677.

Respectfully submitted,

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